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UPPFINNINGENS BENÄMNING: NEW COMPOSITION

5 The present invention relates to novel compositions
for the prevention of symptoms in mammals, which are in-
directly or directly caused by airborne particles. More
particularly, the invention relates to novel compositions
for the prevention and/or reduction of symptoms of allergic
10 rhinitis, upper respiratory tract infections, and "non-
allergic, non-infectious (vasomotor) rhinitis".

Background of the Invention.

15 *Epidemiology.*

Airway diseases caused by exposure to airborne aller-
gens are major health problems to affluent societies. For
example, the prevalence of allergic rhinitis (seasonal,
perennial, and occupational) is 20% or more, and increas-
20 ing. Accordingly, the American Asthma and Allergy Founda-
tion recently reported that about 17 million annual visits
to office-based physicians were attributed to allergic
rhinitis. Also, they reported that 35 million Americans
were allergic to pollen allergens. Besides the morbidity
25 and socioeconomic consequences that these allergies carry
themselves, they have been identified as risk factors for
the development of asthma. Indeed, one way of preventing
the development of bronchial asthma may be to treat the
allergic rhinitis condition.

30 Upper respiratory tract infections (caused by viruses
and bacteria) are also major health problems. For example,
the common cold is a very prevalent disease: The number of
common cold episodes has been estimated to be 5 per year in
the 0-4 year old age group, dropping to 3 episodes per year
35 in the 5-19 year old group. These infections have, notably
in the case of the common cold, been identified as a major

cause of exacerbations of asthma and "chronic obstructive pulmonary disease".

"Non-allergic, non-infectious (vasomotor) rhinitis" is a less prevalent condition (compared with allergic rhinitis and upper respiratory tract infections). Nevertheless, it is a common differential diagnosis of patients having nasal symptoms.

10 *Chemical and physical aspects on disease-producing airborne particles.*

Pollens and allergens themselves, as well as viruses, bacteria, and other exogenous factors, occur as airborne particles. Pollens typically have diameters between 15-60 μm . Virus particles, on the other hand, are typically 15 0.1-0.5 μm in diameter, while the size of bacteria and other prokaryotes ranges widely from 0.1 to about 5 μm . Cigarette smoke, printing ink, and occupational factors, which may produce "non-allergic, non-infectious (vasomotor) rhinitis", may also be viewed as particles with a wide size 20 range. In order to produce disease-processes and symptoms associated with allergic rhinitis, upper respiratory tract infections, and "non-allergic, non-infectious (vasomotor) rhinitis" the disease-producing particles must come in contact with the mucosal surface.

25 *Disease mechanisms and clinical presentations.*

Mechanisms leading to allergic rhinitis comprise the contact of inhaled pollens/allergens with the nasal mucosal lining and the interaction with immunocompetent and inflammatory cells residing in the nasal mucosa. Specific anti- 30 bodies (immunoglobulins) are located at the surface of some of these cells. The allergen cross-bridges with receptors on the cell surface, which results in an activation of these cells and in the release of inflammatory mediators. 35 These mediators, in turn, act on certain cells and structures in the mucosa (e.g., glands, blood vessels, nerve

endings) to produce inflammation and the symptoms of allergic rhinitis, i.e., nasal itching/sneezing, secretions, and blockage.

Upper respiratory tract infections are caused by
5 viruses and bacteria interacting with the mucosa of the upper airways. The most common cause may be rhinoviruses, which bind to specific mucosal receptors, an inflammatory response being produced. This process, in turn, produces symptoms of common cold (sneezing, watery secretions,
10 reduced nasal patency and catarrhal symptoms with accompanying fever and headache).

"Non-allergic, non-infectious (vasomotor) rhinitis" is sometimes caused by airborne particles other than allergens and infectious agents. The pathophysiological
15 processes give rise to a symptomatology that is very similar to that of allergic rhinitis. However, it is less clearly understood.

Established treatments.

20 The best treatment for type-I allergic diseases, such as allergic rhinitis, would be to avoid the allergen. However, this strategy is more or less impossible, particularly for airborne allergens including those carried by pollens. In addition, this line of reasoning applies for
25 infectious agents and particles causing "non-allergic, non-infectious (vasomotor) rhinitis".

There is currently no established pharmacological treatment for upper respiratory tract infections, except for antibiotics and other chemotherapeutics targeting
30 bacteria, antiviral compounds targeting viruses, specifically influenza virus, as well as topical and oral decongestants.

A pharmacological treatment for allergic rhinitis currently comprises topical, oral and systemical glucocorticosteroids, topical and oral antihistamines, topical
35 chromoglycates, oral leukotriene-antagonists, topical and

oral decongestants, topical and oral anticholinergics, and immunotherapy, i.e., repeated exposure to relevant allergens in order to produce a state of increased tolerability. However, there is no single pharmaceutical preparation/treatment available, which treats or reduces all symptoms of allergic rhinitis. The most successful treatment may be topical corticosteroids, but their use is associated with a potential risk of local and systemic adverse effects. Antihistaminic preparations are commonly used, but their efficacy is limited. Local decongestants, though used, are not recommended by physicians skilled in the art.

Antibiotics may be used to treat upper respiratory tract infections caused by bacteria. However, no treatment is available for the common cold (caused by viral infections) except for oral and nasal decongestants (alpha-agonists). The neuraminidase inhibitor zanamivir has recently been introduced for the treatment of Influenza A and B, but its efficacy is limited.

Treatments for "non-allergic, non-infectious (vasomotor) rhinitis" include topical glucocorticosteroids, topical anticholinergics, and topical capsaicin. Common for these treatments, however, is their limited efficacy.

Potentially novel treatments.

An attempt to overcome nasal mucosal exposure of airborne particles, including pollens, is shown in US 6,109,262, a special adhesive nasal filter being used, which physically collects airborne particles. The method and filter disclosed is said to have therapeutic, protective or prophylactic use.

Inter. Arch. Allergy Immunol. 121:85, 2000, teaches the usefulness of regularly applying a mineral oil to the nasal mucosa of patients with seasonal allergic rhinitis in order to reduce allergic symptoms. It is suggested in this document that fatty acids might be helpful in the preven-

tion of allergic rhinitis. Topical application of fats, such as certain triglycerides and oils to the nasal mucosa, has also been marketed for treating dryness of the nasal mucosa (Nozoil®, Pharmacure Health Care AB, Sweden).

5 In DE 20016125 a nasal ointment for prophylaxis of inhalation-allergic reactions, especially hay fever, is shown. The ointment comprises a mixture of saturated hydrocarbons and tannin(s), a mechanical barrier film being formed that prevents allergens from entering the nasal
10 mucosa. Likewise, JP 07258070 depicts a nasal rinsing agent for treating allergic rhinitis. The nose cleaning agent, which consists of an oil/water type of emulsion of pH 3.5-5.5, forms an oil film after spraying into a nasal cavity. As in DE 20016125, the oil is spread on the nasal mucosa
15 and a non-homogenous film is formed.

The attachment of most rhinovirus subtypes to cells depends on a cellular receptor, the intercellular adhesion molecule 1 (ICAM-1). JAMA 1999, May 19; 281(19):1797-804, teaches that recombinant soluble ICAM-1, inhaled as a
20 solution or as a powder, reduces the severity of experimental rhinovirus common colds.

Accordingly, there is an obvious need for new and more efficacious treatments also in this topical area. Furthermore, like for allergic rhinitis, there is a need for
25 a way of preventing or reducing, in a preventive way, the above-mentioned symptoms associated with upper respiratory tract infections, such as common colds.

The Invention.

30 The objective of the invention is to provide a composition, whereby the above-mentioned problems are eliminated.

Another objective of the invention is to provide a composition that is able to capture airborne particles and
35 retard or inhibit their interactions with exterior mucosal membranes.

Still another objective is to provide a composition that has a combined effect of encapsulating airborne particles as well as reducing and/or eliminating the effects of those particles which may reach these membranes.

5 A further objective of the invention is to provide a composition that is sprayable.

These objectives are accomplished by a composition for administration to peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx,
10 which comprises a pharmaceutically effective amount of a locally acting drug and a microemulsion. The microemulsion consists of a non-polar lipid, at least one polar solvent, a surfactant, and a polar lipid.

In the inventive composition, the locally acting drug
15 is mixed with the microemulsion. In this connection, the drug is not intended to be a functional part of the microemulsion or to be slowly released therefrom.

The present invention focuses on those initial stages of the inflammatory process which take place at or in the
20 peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx. For example, at or in the nasal mucosa, an inflammation may result in increased levels of pro-inflammatory chemokines and cytokines, recruitment and activation of specific inflammatory cells,
25 and changes in end-organ functions of the mucosa (e.g., the microcirculation, the secretory apparatus and the ciliary system). Inflammatory processes, although in part characterized by different inflammatory cells, are also associated with upper respiratory tract infections.

30 We have surprisingly found that airborne particles, exemplified by virus, bacteria, pollen, allergens, dust, mould, fungus spores, animal dander, and other solid aerosol particles, can be trapped by the microemulsion of the inventive composition. No similar composition has
35 hitherto been disclosed.

This effect is combined by providing in the composition a locally acting drug. The locally acting drug can be an anti-allergical drug, such as a glucocorticosteroid, an antihistamine, a leukotriene antagonist, a chromoglycate, a decongestant, such as an alpha-agonist, an anti-cholinergic drug, or an anti-infection drug, such as an antibiotic or an anti-viral compound.

In the composition according to the invention the inherent properties of an airborne particle are utilized, i.e. the particle can have a hydrophobic core and is at the same time electrostatically charged. Thereby the particle is conferred hydrophilic properties. However, the charge will immediately be lost when entering the nose and contacting a mucous membrane, which results in that the hydrophobic properties will dominate. Thus, when airborne, such particles (pollens etc.) have a hydrophilic surface which must be substantially captured within a hydrophilic environment. Pure oils will not work, since they can not wet pollens or viruses and thus not encapsulate them.

Microemulsions typically look like clear solutions, but are thermodynamically stable dispersions of one liquid phase into another. The extremely low interfacial tension of the oil/water interphase, the small droplet diameters of approximately 100 nanometers or less as well as water islets of a suitable size, are advantageous properties for capturing airborne particles.

Accordingly, airborne particles can be trapped by the specific self-assembled hydrophilic/hydrophobic structure provided by means of the invention. The microemulsion in the inventive composition is able to provide an environment, which substantially encloses (surrounds) the particles.

Furthermore, a sprayable composition can be provided, which comprises a microemulsion containing large amounts of a polar solvent in order to reduce the viscosity. In addi-

tion, the inventive compositions are able to top spread homogenously on the mucosa and do not only function as a protective barrier but also as a capturing agent for airborne particles, which follows the mucus when swallowed or sneezed out.

The microemulsion of the composition according to the invention is effective for the protection of mucosal membranes that line all body cavities which are open to the exterior. Thus, peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx. can be protected. However, it is preferably used for capturing particles in the nasal cavity, the pharynx, and the larynx.

A microemulsion can be defined as a thermodynamically stable, transparent dispersion of two immiscible liquids, stabilized by an interfacial film of surfactants. In this connection a microemulsion is a clear thermodynamically stable dispersion of two immiscible liquids containing appropriate amounts of surfactants and co-surfactants.

The meaning of surfactant as used in the description and in the claims follows the current usage well known to those skilled in the art. A good surfactant should have a low solubility in both the bulk and dispersed phases of the microemulsion.

The surfactant is usually an organic polymer with a long chain hydrophobic tail and a small hydrophilic head group, and it can be anionic, nonionic, cationic or amphoteric. Nonionic surfactants are preferred since they are less harmful to humans than ionic surfactants.

Suitable nonionic surfactants are polyoxyethylenated alkylphenols (mostly p-octyl-, p-nonyl-, p-dodecyl-, dinonylphenols), polyoxyethylenated straight chain alcohols, polyoxyethylenated polyoxypropylene glycols, polyoxyethylenated mercaptans, long chain carboxylic acid esters (glyceryl and polyglyceryl esters of natural fatty acids, propylene glycol, sorbitol, and polyoxyethylenated sorbitol

esters, polyoxyethylene glycol esters) and alkanolamines (diethanolamine-, isopropanolamine-fatty acid condensates). The edible surfactants are mainly the esters based on glycerol, sorbitol, and propylene glycol.

- 5 Preferably, the surfactant is an amphiphilic compound such as a polysorbate, a poloxamer, or a fatty acid polyoxyethylene. It is most preferred that the amphiphilic compound is polysorbate 80.

- 10 Suitable ionic surfactants are succinic, citric, and diacetyl tartaric acid esters. Lecithin is the preferred surfactant containing a positive charge.

- The required amount of surfactant is dependent on the other components used in the microemulsion of the inventive composition. However, the surfactant concentration should
15 always exceed its critical micellar concentration (CMC).

- The hydrophilic/hydrophobic balance, i.e. the molar ratio of hydrophilic to hydrophobic moieties, has a temperature maximum in the mutual solubility of the surfactant in water and oil. This maximum is adapted to encompass a
20 temperature interval, within which the inventive composition is intended to be used, i.e. around room and body temperatures. Preferably, the hydrophilic-hydrophobic balance of the surfactant, should not exceed 7. Thus, the surfactant comprises 0.1 to 20 % (wt/wt), preferably 1 to
25 10 % (wt/wt) of the microemulsion.

- The surface tension between the two liquid layers of the microemulsion can be further lowered to approach zero by the addition of at least one polar solvent. Thus, the polar solvent may act as a cosurfactant in the microemul-
30 sion of the inventive composition and is preferably a small molecule that improves the stability of the microemulsion system. Increased amounts of polar solvent also reduces the viscosity, a better micro-viscosity being obtained in the microemulsion droplets.

Typical such polar solvents are short chain alcohols, ethanol to butanol, glycols such as propylene glycol, or medium chain alcohols, amines, or acids. Preferred polar solvents are propylene glycols and/or polyethylene glycols and/or a saline solution.

Water and buffered aqueous media can also be used for solubilizing one phase into the other in the microemulsion system, which contain a variety of salts and buffers. Preferably, the salts are alkali and alkaline earth halides, e.g. sodium chloride, potassium chloride, or sodium sulphate. Various buffers may be used, such as citrate, phosphate, HEPES, Tris, or the like to the extent that such buffers are physiologically acceptable for its purpose.

The polar solvent or solvents used in the micro-emulsion of the inventive composition should comprise 5 to 95 % (wt/wt), preferably 10 to 55 % (wt/wt) of the same. It is also preferred that the at least one polar solvent has a pH exceeding pH 5.5.

The polar lipid in the microemulsion can be an alcohol, an amine, cholesterol, a fat soluble vitamin, a glyceride, a phospholipide, a glycolipide, or a sphingolipide, or a mixture thereof. Preferably, the glyceride is a mono-acyl glyceride, for example glyceryl monooleate, glyceryl monolinoleate or glyceryl monolinenoleate.

The polar lipid may comprise 1 to 99 % (wt/wt), preferably 10 to 75% (wt/wt), most preferred 20 to 50 % (wt/wt) of the microemulsion in the inventive composition.

It is an important aspect of the invention that the microemulsion, which consists of a non-polar lipid, at least one polar solvent, a surfactant, and a polar lipid as sole ingredients, provides an environment that substantially encloses airborne particles.

The microemulsion in the inventive composition should also contain one or more non-polar lipids, such as di-acyl glycerides, tri-acyl glycerides, mineral oils, paraffin

oils and esters, as well as ethers or waxes of fatty acids having a total number of carbon atoms more than 22.

Preferably, the non-polar lipid is a tri-acyl glyceride.

Excellent microemulsions are formed by using non-polar oils, such as the normal alkanes, as the non-polar lipid. Triglycerides are preferred because they are edible.

Acceptable animal oils are cod liver oil, lanolin oil, mink oil, orange roughy oil, and shark liver oil. Acceptable vegetable oils include almond, apricot kernel, avocado, castor, coconut, corn, evening primrose, jojoba, olive, safflower, sesame, soybean, and wheat germ oils. Some silicone oils are acceptable, such as certain linear polysiloxanes and cyclic dimethyl polysiloxanes such as cyclomethicone. It is preferred that the vegetable oil is sesame oil.

The non-polar lipid should comprise 1 to 99 % (wt/wt), preferably 5 to 75% (wt/wt), most preferred 5 to 35 % (wt/wt) of the microemulsion.

The composition according to the invention is especially adapted for human use, i.e. to be applied to peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx. for entrapping airborne particles. By using such a composition one delivery device can be used instead of two devices.

The composition can be applied locally. Local applications include for example spray and drops, pipettes made up in single doses, a powder obtained by lyophilization of the emulsion, a tamponage, or a painting. A nasal pool device can be used to apply controlled amounts of the composition on a human nasal airway mucosa. Preferably, a mouth or nasal spray device is used, which contains the inventive composition.

Examples.

The invention will now be further described and illustrated by reference to the following examples. It should

be noted, however, that these examples should not be construed as limiting the invention in any way.

Example 1. Preparation of an exemplary composition.

5 Twenty ml of a microemulsion was prepared, which had the following composition (w/w %):

	Component	Amount (w/w %)
	Glycerol monooleate	34
10	Propylene glycol	23
	Polyethylene glycol 400	18
	Sesame oil	11
	Saline solution	10
	Polysorbate 80	4

15

Example 2. Adverse effects.

The microemulsion according to Example 1 was filled on flasks equipped with a spray mechanism and administered to human volunteers. No signs or complaints of adverse effects were made.

20

Example 3. Prevention of pollen allergy.

In order to test the feasibility of a nasal provocation the microemulsion according to Example 1 was administered to the nasal cavity of 9 subjects by means of a nasal pool device (Greiff L et al. Clin Exp Allergy. 1990 May; 20(3):253-9). Also the placebo (saline solution) was administered with this device.

25

Rinsing was performed by loading and administering 14 ml of saline solution with this nasal pool device.

30

Nasal provocations were performed at two occasions with at least one week in between. The study was of a single blind placebo controlled fashion. At one visit the microemulsion of Example 1 was given and at the other occasion the placebo (isotonic saline). Both treatments

35

(microemulsion and placebo) were given in the nasal pool device (14 ml) in the right nasal cavity.

Before the challenge nasal symptoms were rated, followed by two nasal washings (each, one minute) using the pool device. These washings with 14 ml of saline were undertaken in order to reduce cell free mediators that have been accumulated on the nasal mucosal surface. Thereafter a 5 min saline washing was performed in order to establish a baseline.

The microemulsion and placebo (saline) were delivered by means of the pool device in a randomized order. The treatments (placebo and saline) were being kept in contact with the nasal mucosal surface for 2.5 minutes.

Then the treatment was released and the subjects assessed symptoms once more. Five min after the treatment delivery a nasal allergen challenge with a moderate dose of allergen was given in the same nasal cavity in the same way as the previous washings and treatments had been delivered (right nasal cavity). The subjects performed 10 min after allergen challenge a third symptom assessment and a second 5 min washing was performed as well. Both 5 min washings were collected and immediately cold centrifuged at 2000 rpm and frozen (-18°C) for later analysis.

Nasal symptoms were scored, as previously described, prior to challenge (baseline), immediately before challenge (prior) and 10 min after allergen challenge. Nasal symptoms, runny nose, and blockage were scored 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, 3 = severe symptoms. In addition, the number of sneezes were counted.

Sneezing.

The number of sneezes were determined at baseline, prior to and 10 min after allergen challenge in 9 subjects with pollen allergy after pretreatment with the microemulsion and placebo.

Allergen induces sneezes in the allergic subjects both after microemulsion and placebo treatment with no significant differences between the treatments.

5 *Rhinitis.*

A subjective assessment of nasal secretion was also performed at baseline, prior to and 10 min after allergen challenge, in 9 subjects with pollen allergy after pretreatment with the microemulsion and placebo.

10 Allergen induces nasal secretion in the allergic subjects both after treatment with microemulsion and placebo with no significant differences between the treatments.

15 *Nasal congestion.*

Likewise, a subjective assessment of nasal congestion was performed at baseline, prior to and 10 min after allergen challenge, in 9 subjects with pollen allergy after pretreatment with the microemulsion and placebo.

20 Allergen challenge increases nasal congestion in the allergic subjects both after treatment with microemulsion and placebo. However, the microemulsion significantly reduces nasal congestion as compared to placebo (*= $p < 0.05$).

25 *Total nasal symptom score.*

FIG 1 shows the assessment of total nasal symptom score with reference to sneezing, secretion, and nasal congestion.

30 Allergen challenge increases the total nasal symptom score in the allergic subjects both after treatment with microemulsion and placebo. However, the microemulsion significantly reduces total symptoms as compared to placebo (*= $p < 0.011$).

35

Example 4. Nasal mucosal inflammation.

α 2-Macroglobulin was measured in nasal washings as an index of nasal mucosal inflammation. Samples were collected prior to and 10 min after allergen challenge in 9 subjects with pollen allergy after treatment with the microemulsion according to Example 1 and placebo.

As shown in FIG 2, the allergen challenge induces a significant increase in nasal mucosal output of α 2-macroglobulin after placebo treatment ($*=p<0.01$), but not after treatment with the microemulsion. Furthermore, a significant difference in the levels of α 2-macroglobulin is seen between microemulsion and placebo 10 min after allergen challenge ($*=p<0.05$).

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CLAIMS

1. A composition for administration to peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx. of a mammal, characterized in that it comprises a pharmaceutically effective amount of a locally acting drug and a microemulsion, said microemulsion consisting of a non-polar lipid, at least one polar solvent, a surfactant, and a polar lipid.
2. The composition as in claim 1, characterized in that said polar lipid comprises 20 to 50 % (wt/wt) of said microemulsion.
3. The composition as in claim 1, characterized in that said polar lipid is an alcohol, an amine, cholesterol, a fat soluble vitamin, a glyceride, a phospholipide, a glycolipide, or a sphingolipide, or a mixture thereof.
4. The composition as in claim 3, characterized in that said glyceride is a mono-acyl glyceride.
5. The composition as in claim 4, characterized in that said mono-acyl glyceride is glyceryl monooleate, glyceryl monolinoleate or glyceryl monolinenoleate.
6. The composition as in claim 1, characterized in that said non-polar lipid comprises 5 to 35 % (wt/wt) of said microemulsion.
7. The composition as in claim 1, characterized in that said non-polar lipid is a di-acyl glyceride, a tri-acyl glyceride, a vegetable oil, a mineral oil, a paraffin oil, a paraffin ester, an ether or a wax of fatty acids having a total number of carbon atoms of more than 22.
8. The composition as in claim 7, characterized in that said vegetable oil is sesame oil.

9. The composition as in claim 1, c h a r a c -
t e r i z e d in that said surfactant has a hydrophilic-
hydrophobic balance exceeding 7.

10. The composition as in claim 1, c h a r a c -
5 t e r i z e d in that said surfactant is a polysorbate, a
poloxamer, or a fatty acid polyoxyethylene.

11. The composition as in claim 10, c h a r a c -
t e r i z e d in that said polysorbate is polysorbate 80.

12. The composition as in claim 1, c h a r a c -
10 t e r i z e d in that said at least one polar solvent
comprises 5 to 95 % (wt/wt), preferably 10 to 55 % (wt/wt)
of said microemulsion.

13. The composition as in claim 1, c h a r a c -
t e r i z e d in that said at least one polar solvent has
15 a pH exceeding pH 5.5.

14. The composition as in claim 1, c h a r a c -
t e r i z e d in that said at least one polar solvent
is water, a buffer, a glycol, an alcohol, or a mixture
thereof.

15. The composition as in claim 14, c h a r a c -
20 t e r i z e d in that said at least one polar solvent
is propylene glycol and/or polyethylene glycol and/or
saline solution.

16. The composition as in claim 1, c h a r a c -
25 t e r i z e d in that said locally acting drug is
an anti-allergical drug, a decongestant, or an anti-
infection drug.

17. A mouth or nasal spray device containing the
composition as claimed in claim 1.

ABSTRACT

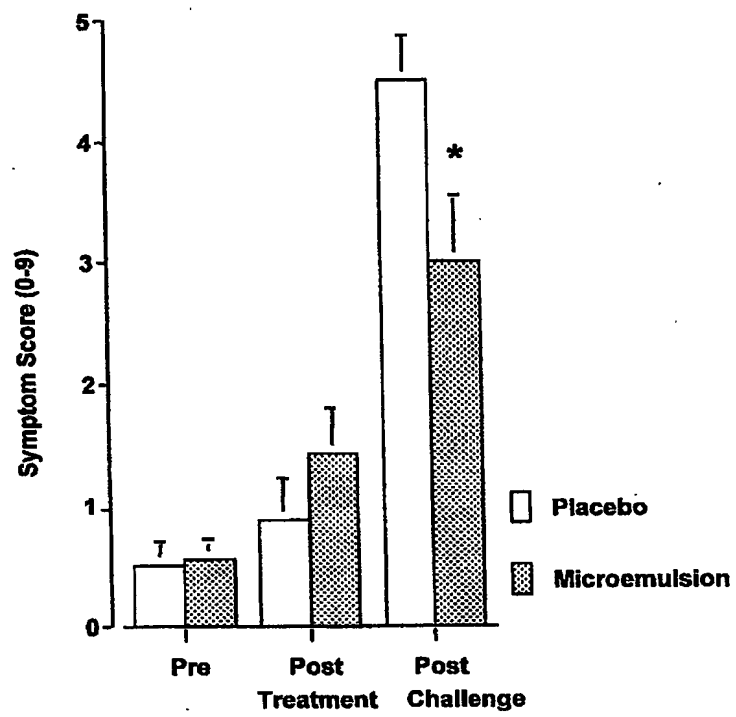
The invention relates to novel compositions for the prevention of symptoms indirectly or directly caused by airborne particles. The compositions comprise a pharmaceutically effective amount of a locally acting drug and a microemulsion, the microemulsion consisting of a non-polar lipid, at least one polar solvent, a surfactant, and a polar lipid. They are intended to be administrated to peripheral membrane linings of the nose, the eyes, the ears, the pharynx, and the larynx. of a mammal, whereby symptoms of allergic rhinitis, upper respiratory tract infections, and "non-allergic, non-infectious (vasomotor) rhinitis" are prevented and/or reduced.

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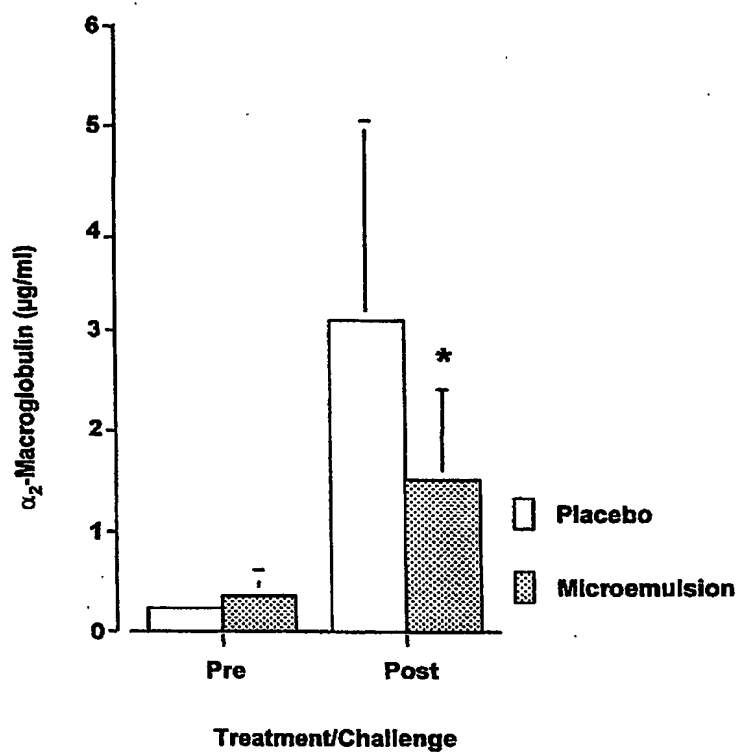
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FIG 1



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FIG 2



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